Reply

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(3) Temporal relationship. (Initiation or enhancement of the event should clearly precede major, ischemia-induced cell death.)

(4) Topographic relationship. (Brain areas that suffer the greatest cell damage should also demonstrate the greatest changes in the event.)

(5) Dose relationship. (Ischemic situations or circumstances that produce greater brain damage should also exhibit larger changes in the event.)

(6) Modulatory neuroprotection. (Inhibiting the event, or otherwise blocking its effects, should decrease the degree of ischemic damage.)

The intracellular events purported to have a role in the pathogenesis of stroke should be considered in the context of this or a similar list. Frequently, when one applies these criteria only to a particular biochemical event, its relationship to the ensuing neuronal damage becomes significantly less clear. For example, one of the earliest events in ischemia is a Ca^{2+}-dependent increase in lipid hydrolytic enzyme activity[3], which includes the formation and accumulation of free fatty acids, such as arachidonic acid, free radicals, thromaboxanes, prostaglandins and leukotrienes. All of these compounds have been suggested to have roles in cell damage and it has been proposed that reducing lipase activity represents a viable means of reducing stroke-related damage. Despite the evidence that free fatty acid accumulation leads to cell death, there are several inconsistencies in this theory. Non-ischemic situations in which free fatty acids accumulate are not associated with cell death[4] and free fatty acid levels can remain unchanged after treatments that attenuate ischemic damage[5]. Moreover, pharmacological inhibition of lipid peroxidation does not completely prevent cell death, suggesting that at best, the accumulation of free fatty acids has a partial role in ischemia-induced cell death[6–10]. A closer examination of the biochemistry of stroke is likely to uncover similar inconsistencies.

Despite the critique of animal models by DeKeyser *et al.*, such experimental tools are fundamentally important in the selection of clinical leads. Although animal models cannot mimic the complex etiology and pathophysiology of human conditions, they do provide a practical way to answer questions concerning biochemistry and function. In the case of stroke, such models can be used to address the specific issues outlined above. Their continued refinement should also be a priority of investigators. Rather than adopting the attitude that models have no predictive value, efforts should be directed at mimicking the human condition, by aiming for a better understanding of the relationship between the biochemical events and cell damage in stroke, and obtaining a detailed assessment of the behavioral effects of the stroke and the effects of treatments on those deficits.

Finally, the authors discussion of the manner in which pharmaceutical companies conduct research and clinical trials is misdirected. The statement 'but there is often so much pressure from senior management in pharmaceutical companies to rush for registration that well-conducted Phase II trials are often neglected' clearly places the blame for clinical failures on the expectations and ethics of corporate management. Are the authors suggesting that given the time and expense to get a drug to the point of Phase II clinical evaluation, that companies would be willing to do less than maximize the possibility of obtaining an accurate measure of the potential of the drug? Do they really mean to suggest that the pressure to gain drug approval forces otherwise excellent researchers to act hastily and unethically? Of course pressure to make decisions exists. It exists because of the time and expense in developing treatments and it exists because individuals need effective treatments. Every effort should be made to determine the potential of a drug in as timely a manner as possible. There are very few second chances and it would be foolish to allow pressure to result in anything other than the best possible trial design at the time. Moreover, as the trials are not conducted by 'senior management', only overseen and financially supported, the authors criticism seems too narrowly directed.

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Reply

Emerich correctly points out that not all of the biochemical events that occur during focal brain ischaemia contribute to cell death[1]. Some events might be merely epiphenomena. However, the compounds that have been investigated in pivotal clinical trials were selected on the basis of their neuroprotective properties in preclinical experiments. The animal models are therefore indispensable. Nevertheless, one should not expect anything more from these animal models than an indication that a compound has neuroprotective properties, and we sincerely believe that all efforts directed at mimicking the human condition are a waste of time and money. The animal experiments should not necessarily be predictive for the human situation.

Emerich is also correct in stating that every effort should be made to determine the potential of a drug in as timely a manner as possible. Once the neuroprotective properties and an acceptable safety profile of a compound have been established, one should immediately go to so called 'proof of concept' studies in individuals who have suffered a stroke. This implies that adequate Phase II studies must be carried out to determine the optimal tolerated dosages, therapeutic time window and duration of therapy. Such information can now be obtained from a small number of individuals by using imaging techniques that visualize a potentially salvageable penumbra, such as combined diffusion weighted and perfusion MRI (Ref. 2). We should maximally exploit these tools in order to design Phase III trials that have a better chance of success.

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